REMARKS

In the Office Action of September 14, 2006, Claims 28-39 were rejected under 35 U.S.C. § 103(a). Claim 28 is herein amended, without prejudice or disclaimer of the subject matter contained therein, to remove the limitations added in the Office Action Response dated June 15, 2006, in view of the Examiner's statements in the Office Action dated September 14, 2006, that such amendments did not confer patentability to the claim. Each of the specific rejections is addressed below.

Rejections under 35 U.S.C. § 103(a)

Claims 28 and 32-35

The Examiner has rejected claims 28 and 32-35 under 35 U.S.C. § 103(a) as being unpatentable over Ellington *et al.* (1992) Nature 355:850-852 in view of Hilvert *et al.* (U.S. Pat. No. 5,208,152). Regarding independent claim 28, the Examiner asserts that Ellington *et al.* teach a method of obtaining single-stranded DNA molecules capable of ligand binding that are isolated via selection and amplification *in vitro*. In addition, Ellington *et al.* teach that nucleic acid aptamers may be new catalysts for chemical transformations that are analogous to catalytic antibodies. The Examiner asserts that the '152 patent teaches the use of a catalytic antibody to perform a Diels-Alder reaction. The Examiner further asserts that this reference teaches that it would be beneficial to find a specific catalyst for Diels-Alder reactions. From these references, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the ligand binding nucleic acid apatmers of Ellington *et al.* to couple with a first reactant and catalyze the Diels-Alder reaction with a free reactant to produce a cyclohexene derivative product library. Regarding dependent claims 32-35, the Examiner asserts that Ellington *et al.* teach the use of DNA oligomers having conserved and random sequences (claim 32), the use of single stranded DNA (claim 33), and that different single stranded-DNA oligomers can be selected to fold into specific binding structures (claims 34 and 35). The Examiner also rejected Applicants' arguments made in Applicants' previous Office Action response.

The Examiner bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. In determining obviousness, one must focus on Applicant's invention as a

whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ2d 1241,1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). To establish obviousness, both the elements of the claimed invention plus the motivation to combine the elements must be present in the prior art. *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (PTO Bd. App. Intf., 1988). Thus, if an element recited in the claims is not described in the cited prior art references, then *prima facie* obviousness is not established.

Additionally, even if all of the elements of the instant claims are present in the cited references, (which Applicant does not admit), there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings AND there must be reasonable expectation of success.

Applicants traverse the Examiner's rejection. To summarize Applicants' first argument, Applicants note that not all of the elements of the instant claims are taught by the references; specifically, the instant claims are directed to reactants coupled to nucleic acid ligands such that the nucleic acid ligands act **non-catalytically**. In contrast, the cited references teach that the active molecules achieve their results via catalytic action.

Specifically, Applicants note that Hilvert teaches the use of catalytic antibodies to catalyze the Diels-Alder reaction; and that Ellington *et al.* suggest that DNA can act catalytically. Key to these references' teachings is the fact that both active species act catalytically. Applicants respectfully direct the Examiner's attention to the definition of "catalyst" as understood by one of skill in the art. Specifically, in chemistry and biology, catalysis is the acceleration (increase in rate) or slowing down of a chemical reaction by means of a substance, called a catalyst, **that is itself not consumed by the overall reaction**. Catalysts participate in reactions but **are neither reactants nor products of the reaction that they catalyze**. Catalysts work by providing an alternative pathway for the reaction to occur, thus reducing the activation energy and increasing the reaction rate.

In the Examiner's rejection the Examiner states that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method comprising using catalytic antibodies for Diels-Alder reactions as taught by Hilvert *et al.* with the ligand binding nucleic acids as taught by Ellington *et al.* with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in **providing new catalysts** for chemical transformations." (Office Action, page 4) (emphasis added). In other words, the Examiner is asserting that the instant invention teaches nucleic acids acting as "catalysts".

Applicants respectfully submit that the Examiner is mistaken in his assertion that the nucleic acid ligands of the instant invention act catalytically. As discussed above, catalysts are not consumed in the reaction that they catalyze. Applicants, in the instant specification, teach that their nucleic acids act to facilitate (n.b., Applicants note that the word used is "facilitate" not "catalyze") reactions, such as a Diels-Alder reaction. Applicants' method does not include the nucleic acid being released from the products during the reaction to bind to new reactants. See, e.g., Fig. 2A-2D; page 30, lines 18-20 ("products having predetermined desirable characteristics can be partitioned away from the rest of the product library **while still attached to the nucleic acid which facilitated their formation** by various methods known to one of ordinary skill in the art.") (emphasis added) Applicants' nucleic acids thus remain bound to the products generated following the reaction. As discussed above, "catalysts", by definition, as known by one of skill in the art, are not bound to products and are not consumed in the reaction. In contrast, the nucleic acids of the instant invention are not catalysts, as they remain bound to the reaction products, and are thus consumed in the reaction that forms the products.

Thus, the references fail to teach or suggest a nucleic acid molecule that is used in a non-catalytic manner to facilitate a method for producing a cyclohexene derivative product library in accordance with claim 28 and dependent claims 32-35. Accordingly, not all of the elements of the instant claims are present in the references and thus Applicants submit that a *prima facie* case of obviousness is not properly made out by the Examiner. Reconsideration is respectfully requested.

Additionally, even if all of the elements of the instant claims are present in the cited references, (which Applicant does not admit), there must be some suggestion or motivation,

either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings AND there must be reasonable expectation of success. Applicant submits that these tests for obviousness fail as well, as applied to the instant claims. The references' teachings include Hilvert's teaching of the use of antibodies that have been formed using an antigen that mimics the transition state of the Diels-Alder reaction in order to catalyze the Diels-Alder reaction, as well as Ellington *et al.*'s teaching of selection of single stranded DNA molecules that fold into specific ligand-binding structures, thus predicting the possibility of these DNA molecules acting catalytically to catalyze reactions. If Applicants assume, *arguendo*, that these teachings rise to the level of a suggestion and/or give rise to a reasonable expectation of success, (as is stated in the Examiner's rejection) that a catalytic nucleic acid may be generated that can catalyze a reaction that includes the Diels-Alder reaction, such teachings do not provide a motivation or a reasonable expectation of success for a **non-catalytic** nucleic acid to catalyze a reaction including a Diels-Alder reaction.

Accordingly, Applicants respectfully submit that the references do not provide a reasonable expectation of success for the invention of claim 28 and dependent claims 32-35, and thus Applicants submit that a *prima facie* case of obviousness is not properly made out by the Examiner for the reasons discussed above. Reconsideration is respectfully requested.

Claims 29 and 36-39

The Examiner has rejected claim 29 and claims 36-39 under 35 U.S.C. § 103(a) as being unpatentable over Ellington *et al.* in view of Hilvert *et al.* and further in view of Verdine (PCT International Publication No. WO 93/14108). Claim 29 of the instant invention is drawn to the method of claim 28 further comprising a linker group between the first reactant and the nucleic acid. Claim 36 of the instant invention is drawn to the method of claim 28 wherein nucleic acid test mixture comprises nucleic acids having one or more functional groups as set forth in the claim. Claims 37 to 39 are drawn to the method of claim 36 wherein the functional group is positioned at the ribose ring (claim 37), the base (claim 38) or the phosphate group (claim 39). Verdine is cited as teaching the use of linker groups between nucleic acids and first reactants, and also the attachment of functional groups at various positions of nucleic acids including the ribose position, the base of the nucleic acid and the phosphate group.

As discussed in detail above, the Ellington *et al.* reference taken either alone or in combination with Hilvert does not teach or suggest the method of this invention. Specifically, Hilvert in combination with Ellington *et al.* fail to teach or suggest a nucleic acid molecule that is used in a non-catalytic manner to facilitate a method for producing a cyclohexene derivative product library in accordance with claim 28. Further, Hilvert in combination with Ellington *et al.*'s teachings do not provide a motivation or a reasonable expectation of success for a **non-catalytic** nucleic acid to catalyze a reaction including a Diels-Alder reaction. Verdine does not remedy these deficiencies. Accordingly, Applicants submit that a *prima facie* case of obviousness for claims 29, 36-39 is not properly made out by the Examiner. Reconsideration is respectfully requested.

Claims 30 and 31

The Examiner has rejected claims 30 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Hilvert *et al.* (U.S. Patent No. 5,208,152), Ellington *et al.* (Nature, 1992: 355, pp. 850-852) and Verdine (PCT International Publication Number WO 93/14108) as applied to claim 29 above, and in further view of Cload *et al.* (J. Am. Chem. Soc., 1993, 115, pp 5005-5014) as evidenced by Jolly (Modern Inorganic Chemistry, 1984, McGraw Hill).

Claim 30 of the instant invention is drawn to the method of claim 29 wherein the linker has a size in the range of 10 to 1000 Å and claim 31 is drawn to the method of claim 30 wherein said linker is selected from PEG, polyvinyl alcohol, polyacrylates and polypeptides. The Examiner reasons that Cload *et al.* teach the use of oligonucleotide probes tethered to a PEG linker (claim 31) and the combination of Jolly and Cload *et al.* clearly establish the length of the linker taught by Cload *et al.* as being between 10 and 1000 Å (claim 30). As discussed in detail above, the Ellington *et al.* reference taken either alone or in combination with Hilvert does not teach or suggest the method of this invention. Specifically, Hilvert in combination with Ellington *et al.* fail to teach or suggest a nucleic acid molecule that is used in a non-catalytic manner to facilitate a method for producing a cyclohexene derivative product library in accordance with claim 28. Further, Hilvert in combination with Ellington *et al.*'s teachings do not provide a motivation or a reasonable expectation of success for a **non-catalytic** nucleic acid to catalyze a reaction including a Diels-Alder reaction. Applicants respectfully submit that Verdine, Cload, and Jolly do not remedy these deficiencies. Accordingly, Applicants submit that

a *prima facie* case of obviousness for claims 30-31 is not properly made out by the Examiner. Reconsideration is respectfully requested.

Applicant believes that the pending claims are now in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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